

COMPOSITIONS OF CRACC FUSIONS AND METHODS FOR MODULATING AN IMMUNE RESPONSE AGAINST CANCERS, INFECTIONS DISEASES AND DISORDERS

RELATED APPLICATION

[0001] This application claims the benefit of priority to U.S. Provisional Patent Application No. 62/732,975, filed Sep. 18, 2018, which is hereby incorporated by reference in its entirety.

GOVERNMENT SUPPORT

[0002] This invention was made with government support under AI122808 awarded by the National Institutes of Health. The government has certain rights in the invention.

BACKGROUND

[0003] Despite expression of altered oncogenic proteins expressed by tumor cells, which should be recognized by T cell as non-self and thereby induce immune responses, the local tumor immunosuppressive environment can prevent anti-tumor immune activity by inhibition of T cells directly or indirectly via soluble factors or by reduction of co-stimulation signals from antigen presenting cells (APCs) (Adler A J et al. *Curr Cancer Drug Targets* 2007; 7(1):3-14; Gabrilovich D I et al. *Nat Rev Immunol.* 2012; 12(4):253-68; Juneja V R et al. *J Exp Med.* 2017; 214(4):895-904). Immunomodulatory monoclonal antibodies targeting negative T cell receptors, such as CTLA-4 (Hodi F S et al. *N Engl J Med.* 2010; 363(8):711-23), PD-1 (Topalian S L et al. *N Engl J Med.* 2012; 366(26):2443-54), Tim-3 (Anderson A C et al. *Immunity* 2016; 44(5):989-1004), and others, have proven to be effective anti-tumor therapies via blockade of these inhibitory T cell receptors. Furthermore, agonists against co-stimulatory receptors targeting APCs, such as CD134 (OX40) (Weinberg A D et al. *Immunol Rev.* 2011; 244(1):218-31), CD137 (4-1BB) (Ascierto P A et al. *Semin Oncol.* 2010; 37(5):508-16), and CD27 (Roberts D J et al. *J Immunother.* 2010; 33(8):769-79), are promising therapies that will allow for enhanced antigen cross-presentation, T cell activation and increased tumor killing. A combination of multiple immune checkpoint inhibitors has been shown to be superior to using a mono-targeted approach alone (Larkin J et al. *N Engl J Med.* 2015; 373(1):23-34; Moynihan K D et al. *Nat Med.* 2016; 22(12):1402-10; Ryan J M et al. *Cancer Immunol Immunother.* 2018; 67(4):605-13), allowing for a strengthened immune response against tumors and potentially preventing relapse in the future. Therefore, finding additional targets for enhancing anti-tumor responses to use as stand-alone therapies or in combination with others is of interest.

SUMMARY

[0004] Numerous embodiments are described herein that can be applied to any aspect of the present invention or embodiment thereof.

[0005] One aspect of the invention relates to a method for treating or preventing cancer in a subject in need thereof comprising administering to the subject an effective amount of at least one CRACC composition, said composition comprising a non-naturally occurring vector comprising:

[0006] i) a nucleic acid sequence encoding the amino acid sequence of at least one CD2-like receptor activating cyto-

toxic cell gene (CRACC) fusion, which has at least 50% sequence identity to the amino acid sequence set forth in Table 5;

[0007] ii) a nucleic acid sequence of a CRACC fusion, which has at least 50% sequence identity to the nucleotide sequence set forth in Table 6;

[0008] iii) a nucleic acid sequence encoding the amino acid sequence of at least one extracellular domain (ECD) of CRACC, which has at least 50% sequence identity to the amino acid set forth in Table 1; said ECD is linked to a nucleic acid sequence encoding the amino acid sequence of at least one Fc constant region or Fc constant domain (Fc), which has 50% sequence identity to the amino acid sequence set forth in Table 3; or

[0009] iv) a nucleic acid sequence of at least one ECD of CRACC, which has at least 50% sequence identity to the nucleotide sequence set forth in Table 2; said ECD is linked to a nucleic acid sequence of at least one Fc, which has 50% sequence identity to the amino acid sequence set forth in Table 4;

[0010] to thereby treat or prevent cancer in the subject.

[0011] Another aspect of the invention relates to a method for treating or preventing a pathogenic infection in a subject in need thereof comprising administering to the subject an effective amount of at least one CRACC composition, said composition comprising a non-naturally occurring vector comprising:

[0012] i) a nucleic acid sequence encoding the amino acid sequence of at least one CRACC fusion, which has at least 50% sequence identity to the amino acid sequence set forth in Table 5;

[0013] ii) a nucleic acid sequence of a CRACC fusion, which has at least 50% sequence identity to the nucleotide sequence set forth in Table 6;

[0014] iii) a nucleic acid sequence encoding the amino acid sequence of at least one ECD of CRACC, which has at least 50% sequence identity to the amino acid set forth in Table 1; said ECD is linked to a nucleic acid sequence encoding the amino acid sequence of at least one Fc, which has 50% sequence identity to the amino acid sequence set forth in Table 3; or

[0015] iv) a nucleic acid sequence of at least one ECD of CRACC, which has at least 50% sequence identity to the nucleotide sequence set forth in Table 2; said ECD is linked to a nucleic acid sequence of at least one Fc, which has 50% sequence identity to the amino acid sequence set forth in Table 4;

[0016] to thereby treat or prevent a pathogenic infection in the subject.

[0017] Another aspect of the invention relates to a method of modulating an immune response in a subject in need thereof comprising administering to the subject an effective amount of at least one CRACC composition, said composition comprising a non-naturally occurring vector comprising:

[0018] i) a nucleic acid sequence encoding the amino acid sequence of at least one CRACC fusion, which has at least 50% sequence identity to the amino acid sequence set forth in Table 5;

[0019] ii) a nucleic acid sequence of a CRACC fusion, which has at least 50% sequence identity to the nucleotide sequence set forth in Table 6;

[0020] iii) a nucleic acid sequence encoding the amino acid sequence of at least one ECD of CRACC, which has at